CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208742Orig1s000

CHEMISTRY REVIEW(S)

QUALITY ASSESSMENT

Recommendation: Approval

NDA 208742
Review #3
Nov 28, 2018

Drug Name/Dosage Form	Dexamethasone Ophthalmic Insert
Strength	0.4 mg
Route of Administration	Intracanalicular
Rx/OTC Dispensed	Rx
Applicant	Ocular Therapeutix Inc
US agent, if applicable	N/A

SUBMISSION(S) REVIEWED	DOCUMENT DATE
Resubmission	28-Jun-2018

Quality Review Team

DISCIPLINE	Reviewer	BRANCH/DIVISION
Drug Substance	Rohit Tiwari	ONDP//DNDAPI/NDBI
Drug Product	Chunchun Zhang	ONDP/DNDP-I/Branch III
Process	Vidya Pai	OPF/DIABIII
Microbiology	Daniel Schu	OPF/DMA/MABIII
Facility	Vidya Pai	OPF/DIABIII
Biopharmaceutics	Om Anand	ONDP/DB/Branch I
Regulatory Business Process Manager	Kristine Leahy	OPRO/DRBPMI/RBPMBI
Application Technical Lead	Chunchun Zhang	ONDP/DNDP-I/Branch III
Laboratory (OTR)	NA	
ORA Lead	Paul Perdue	ORA/OO/OMPTO/DMPTPO/MDTP
Environmental Assessment (EA)	Chunchun Zhang	ONDP/DNDP-I/Branch III

Quality Review Data Sheet

1. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	STATUS	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	Type II	(b) (4)	(b) (4)	Adequate	9/28/ 2018	LoA: 4/11/2012. Reviewed by Rohit Tiwari.

B. Other Documents: *IND, RLD, or sister applications*

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	114720	This product during IND development

2. CONSULTS: NA

Executive Summary

I. Recommendations

Satisfactory information and responses have been submitted to support the quality of Biopharmaceutics, drug substance, drug product and quality micro aspects; refer to IQA#1 dated 6/17/2017 and IQA# 2 dated 7/5/2017. Drug product and quality micro upholds the approval recommendations after evaluating this resubmission. All the deficiencies are found acceptable from manufacturing process perspective.

The outcome of the most recent inspection of drug product manufacturing facility (Ocular Therapeutix Inc) for this resubmission has resulted in Office of Process and Facilities recommending Approval. An overall acceptable recommendation for all the facilities was issued on 11/28/2018. Therefore, NDA 208742 is recommended Approval from Product Quality perspective.

Labeling recommendations from the Product Quality perspective will be provided to the OND PM for consideration during final labeling.

I. Summary of Quality Assessments

A. Drug Substance [Dexamethasone] Quality Summary

The applicant cross-referenced the CMC information for the drug substance to DMF (b) (4) DMF (b) (4) was found adequate by Rohit Tiwari on 9/28/2018.

B. Drug Product [Dexamethasone Insert] Quality Summary

Dexamethasone intracanalicular insert drug product is (b) (4) yellow (b) (4) with no visible foreign particulate matter 3mm cylindrical shaped insert in a foam insert (b) (4) within a (b) (4) foil pouch.

All excipients used in the formulation are adequately qualified. No novel excipients are used in the formulation. The drug product specification includes tests for appearance, identification, assay, impurity, dry dimension, content uniformity, expansion, equilibrium diameter, in vitro release, water content, visibility, endotoxin and sterility. The drug product release specification has included three additional testing including visible particulate, subvisible particulate matter, and NHS limit in this resubmission. The specification is acceptable. All analytical methods are described in reasonable detail and have been adequately validated.

Based on the review of the current process parameters, controls and development results to date, there are no outstanding concerns from manufacturing process perspective. Quality micro has found the sterility assurance acceptable.

A preapproval inspection for Ocular Therapeutix, Inc., FEI#3008477155, the drug product manufacturing site, was made during this review cycle to support the application. Based on the inspection, and review of the firm's responses to the inspectional observations, the firm appears to have in place adequate quality oversight; manufacturing and process controls to support this submission. OPF issued an overall acceptable recommendation for all the facilities in Panorama on 11/28/2018.

The applicant has updated the stability with 36 months at 5°C for three primary registration batches (10141303, 07031401 and 07171404). Additionally, 12 months stability data at 5°C and 3 months at 25°C/60%RH for another three registration batches (11071603, 11171601 and 11301601) at commercial scale are provided in this resubmission. There is no trend observed on all the test parameters when the drug products were stored at long term storage condition (5°C) [redacted] (b) (4).

A shelf-life of 36 months when stored under refrigerated conditions (5°C) [redacted] (b) (4) is granted for the drug product.

C. Summary of Drug Product Intended Use

Proprietary Name of the Drug Product	DEXTENZA
Non Proprietary Name of the Drug Product	Dexamethasone ophthalmic insert
Non Proprietary Name of the Drug Substance	Dexamethasone
Proposed Indication(s) including Intended Patient Population	Treatment of ocular pain associated with ophthalmic surgery
Duration of Treatment	NA
Maximum Daily Dose	0.4 mg
Alternative Methods of Administration	NA

D. Any Special Product Quality Labeling Recommendations: None

E. Life Cycle Knowledge Information

From Initial Risk Identification			Review Assessment		
Attribute/ CQA	Factors that can impact the CQA	Initial Risk Ranking	Risk Mitigation Approach	Final Risk Eval.	Lifecycle Considerations Comments
Sterility	• Formulation • Container closure[1] • Process parameters • Scale/equipment • Site	H	No preservative [redacted] (b) (4) sterilization has been validated. Sterility assurance is included in the release drug product specification.	H	Post-approval stability protocol[2] will test sterility.

Endotoxin Pyrogen	• Formulation • Container closure[1] • Process parameters	H	Endotoxin testing will be performed at release.	L	Endotoxin testing will be performed at release on stability.
Assay (API), stability	• Formulation • Container closure[1] • Raw materials	L	Robust analytical method validated for assay; no trend on stability; levels remain within the proposed specification. Label claim will be delivered.	L	
Assay (preservative)	• Formulation • Container closure[1] • Process parameters • Scale/equipment	L	No preservative. Single use.	L	
Uniformity of Dose	• Formulation • Container closure[1] • Process parameters • Scale/equipment	H	Content uniformity is included in the drug product release specification.	L	
Osmolality	• Formulation • Container closure[1] • Process parameters • Scale/equipment	L	The drug product is an insert. Not relevant.	L	
pH	• Formulation • Container closure[1] • Process parameters • Scale/equipment	L	The drug product is an insert. Not relevant.	L	
Particulate matter	• Formulation • Container closure[1] • Process parameters • Scale/equipment	M	Per ophthalmic product requirements, particulate matter is controlled in the drug specification with no for foreign particulate matter.	L	
In vitro drug release	• Formulation	H	An in vitro release test is included in the drug product specifications. The acceptance criteria were modified to better capture the release profile. The in vitro release method can detect changes in the drug product that occur upon storage at a higher temperature. In addition, the in vitro release method is discriminating with regard to the drug loading in the gel.	L	

1 Stability studies demonstrate container closure compatibility with the drug product for all quality attributes.

2 Post-approval stability protocol provides for testing of all quality attributes.

Primary Quality Review

ASSESSMENT OF Drug Substance

Adequate. Refer to Review #1 dated on 6/17/2016 and 7/5/2017.

ASSESSMENT OF THE BIOPHARMACEUTICS INFORMATION

Adequate. Refer to Review #1 dated on 6/17/2016.

ASSESSMENT OF ENVIRONMENTAL ANALYSIS

Adequate. Refer to Review #1 dated on 6/17/2016.

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MICROBIOLOGY

Product Background:

NDA: 208742

Drug Product Name / Strength: Dextenza™ (b) (4) Dexamethasone Intracanalicular (b) (4); 0.4 mg/implant; single-use

Route of Administration: Intracanalicula (b) (4)

Applicant Name: Ocular Therapeutix, Inc.

Manufacturing Site: Ocular Therapeutix
36 Crosby Drive, Suite 101
Bedford, MA 01730

Method of Sterilization: (b) (4) sterilization

Review Recommendation: **Adequate**

Theme (ANDA only): **N/A**

Justification (ANDA only): N/A

Review Summary: See remarks.

List Submissions Being Reviewed: Seq 0041 (06/28/2018); Seq 0045 (09/20/2018)

Highlight Key Outstanding Issues from Last Cycle: N/A.

Remarks: The submission is in response to the Agency's 10 July Complete Response Letter. Sterility assurance information was previously found adequate from a Product Quality Microbiology perspective (See Microbiology Review of NDA 208742 (208742.doc), dated 20 May 2016); however, updated information has been provided in this submission (i. (b) (4) sterilization process and updated stability protocol/data) which is reviewed here. The drug product is a dried hydrogel that is loaded in a foam insert, which i (b) (4) within a foil pouch (b) (4) deficiency was conveyed to the applicant in an Information Request, dated 13 September 2018. The applicant's response to the Information Request was received on 20 September 2018.

The submission is recommended for approval from the standpoint of product quality microbiology.

Concise Description Outstanding Issues Remaining: N/A.

Supporting Documents:

- Microbiology Review of NDA 208742 (208742.doc), dated 20 May 2016, for sterility assurance information reviewed in the 1st review cycle and deemed adequate.

List Number of Comparability Protocols (ANDA only): N/A.

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(b) (4)

[redacted]

Primary Microbiology Reviewer Name and Date: Daniel J. Schu, Ph.D., 09/24/2018

Secondary Reviewer Name and Date (and Secondary Summary, as needed):
Julie Nemecek, Ph.D., 09/24/2018
"I concur."

Daniel Schu

Digitally signed by Daniel Schu
Date: 9/24/2018 09:30:32PM
GUID: 55919d6300e16b08a5f33c77046bd421

Julie Nemecek

Digitally signed by Julie Nemecek
Date: 9/25/2018 07:11:21AM
GUID: 5277e82100088e39e79f3393e72134cf

Chunchun Zhang

Digitally signed by Chunchun Zhang
Date: 11/28/2018 05:27:41PM
GUID: 51269608000064178e75377202fe6c5d

Recommendation: Complete Response

NDA 208742
Review #2
July 5, 2017

Drug Name/Dosage Form	Dexamethasone Ophthalmic Insert
Strength	0.4 mg
Route of Administration	Intracanalicular
Rx/OTC Dispensed	Rx
Applicant	Ocular Therapeutix Inc
US agent, if applicable	N/A

SUBMISSION(S) REVIEWED	DOCUMENT DATE
Resubmission	19-Jan-2017

Quality Review Team

DISCIPLINE	Reviewer	BRANCH/DIVISION
Drug Substance	Rohit Tiwari	ONDP//DNDAPI/NDBI
Drug Product	Chunchun Zhang	ONDP/DNDP-I/Branch III
Process	Vidya Pai	OPF/DIABIII
Microbiology	Daniel Schu	OPF/DMA/MABIII
Facility	Vidya Pai	OPF/DIABIII
Biopharmaceutics	Om Anand	ONDP/DB/Branch I
Regulatory Business Process Manager	Kristine Leahy	OPRO/DRBPMI/RBPMBI
Application Technical Lead	Chunchun Zhang	ONDP/DNDP-I/Branch III
Laboratory (OTR)	NA	
ORA Lead	Paul Perdue	ORA/OO/OMPTO/DMPTPO/MDTP
Environmental Assessment (EA)	Chunchun Zhang	ONDP/DNDP-I/Branch III

Quality Review Data Sheet

1. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	STATUS	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	Type II	(b) (4)	(b) (4)	Adequate	June 23, 2017	LoA: 4/11/2012. Reviewed by Rohit Tiwari.

B. Other Documents: *IND, RLD, or sister applications*

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	114720	This product during IND development

2. CONSULTS:

DISCIPLINE	STATUS	RECOMMENDATION	DATE	REVIEWER
Biostatistics	NA			
Pharmacology/Toxicology	Adequate		6/21/2017	Andrew McDougal
CDRH	NA			
Clinical	NA			
Other	NA			

Executive Summary

I. Recommendations

Satisfactory information and responses have been submitted to support the quality of biopharmaceutics and quality micro aspects; refer to IQA#1 dated 6/17/2017. Drug substance and drug product Reviews #1 recommended Approval and Reviews #2 upholds the approval recommendations after evaluating this resubmission. There are three non-CR IRs for the manufacturing process and therefore the manufacturing process is deemed deficient.

The original NDA was issued a complete response due to GMP non-compliance of the drug product manufacturing facility.
The outcome of the most recent inspection of drug product manufacturing facility (Ocular Therapeutix Inc) for this resubmission has once again resulted in Office of Process and Facilities recommending Withhold. Therefore, NDA 208742 is recommended Complete Response from Product Quality perspective.

Labeling recommendations from the Product Quality perspective will be provided to the OND PM for consideration during final labeling.

A. Recommendation and Conclusion on Approvability

1. Summary of Complete Response issues: As described above.

2. Action letter language, related to critical issues such as expiration date: The following CR statements on the unacceptable status of the manufacturing facility (Ocular Therapeutix Inc.) should be included in the CR letter:
   *During a recent inspection of the **Ocular Therapeutix, Inc., FEI#3008477155**, manufacturing facility for this application, our field investigators conveyed deficiencies to the representatives of this facility. Satisfactory resolution of these deficiencies is required before this application may be approved.*

   The following non-CR comments should be included in the CR letter:
   1. As yield specifications may be further tightened based on additional batch history and yield improvement initiatives, please tighten yield limits for visual inspection (Percent Actual yield (Step#11.13)) and Percent yield for the batch (Step#11.33).

   2. Update your visual inspection controls to include risk based defect categorization with related acceptable quality limits (AQL) and justification for the limits.

   3. Provide a comprehensive list of manufacturing, equipment and procedural changes and controls put in place since the previous re-submission to address inspectional deficiencies. Provide the updated batch manufacturing instructions and any new production records supporting this NDA for our review.

3. Benefit/Risk Considerations: Not applicable for CR.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

II. Summary of Quality Assessments

A. Drug Substance [Dexamethasone] Quality Summary

The applicant cross-referenced the CMC information for the drug substance to DMF (b) (4). DMF (b) (4) was found adequate by Rohit Tiwari on 6/23/2017.

B. Drug Product [Dexamethasone Insert] Quality Summary

Dexamethasone intracanalicular insert drug product i (b) (4) yellow (b) (4) with no visible foreign particulate matter 3mm cylindrical shaped insert in a foam inser (b) (4) l within a (b) (4) foil pouch.
All excipients used in the formulation are adequately qualified. No novel excipients are used in the formulation. The drug product specification includes tests for appearance, identification, assay, impurity, dry dimension, content uniformity, expansion, equilibrium diameter, in vitro release, water content, visibility, endotoxin and sterility. The specification is acceptable. All analytical methods are described in reasonable detail and have been adequately validated. The applicant has performed automatic integration instead of manual integration for assay, impurity, in-vitro release rate and content uniformity analytical methods in this resubmission, the comparability results indicate that there is no difference between manual and automatic integrations.

In this resubmission, batch analyses data are provided for 3 commercial batches of drug product in the commercial container closure system at commercial scale of (b) (4) units. All batches complied with the proposed specification.

No stability update was submitted in this resubmission. The original NDA submission provided eighteen months of stability data for one registration batch and twelve months of stability data for the other two registration batches at long term condition (5°C) at 74% of commercial scale. No accelerated stability data is submitted in the NDA. There is no trend observed for all the test parameters when the drug products were stored at long term storage condition (5°C). These results which included statistical analysis supports both the expiration dating period and storage statement listed below.

1. Strength: 0.4 mg
2. Description/Commercial Imag (b) (4) yellow (b) (4) with no visible foreign particulate matter 3mm cylindrical shaped insert.
3. Summary of Product Design: Dexamethasone intracanalicular insert
4. List of Excipients: See Drug Product Review #1.
5. Process Selection (Unit Operations Summary)
    a. Sterilization processes of the drug product, as applicable

(b) (4)

(b) (4)

b. Critical equipment: NA

6. Container Closure: In a foam inser (b) (4) within (b) (4) (b) (4) foil pouch.
7. Expiration Date & Storage Condition (b) (4) months with the storage statement of stored 2°C – 8°C and a cautionary statement, "protect from light".
8. List of co-packaged components: None

C. Summary of Drug Product Intended Use

Proprietary Name of the Drug Product	DEXTENZA
Non Proprietary Name of the Drug Product	Dexamethasone ophthalmic insert
Non Proprietary Name of the Drug Substance	Dexamethasone
Proposed Indication(s) including Intended Patient Population	Treatment of ocular pain associated with ophthalmic surgery
Duration of Treatment	NA
Maximum Daily Dose	0.4 mg
Alternative Methods of Administration	NA

D. Biopharmaceutics Considerations

Dextenza™ (b) (4) dexamethasone) Insert is indicated for the treatment of ocular pain associated with ophthalmic surgery. Dextenza is a dexamethasone intracanalicular insert drug product [0.4 mg strength] that is inserted into the canaliculus following ophthalmic surgery. The Biopharmaceutics review evaluated the acceptability of the in vitro release method, the in vitro release acceptance criteria (b) (4)

In Vitro Release Method: ACCEPTABLE

The following in vitro release method is acceptable:

Apparatus	Medium	Medium Volume	Temperature	Shaking/stirring
125-mL polypropylene bottle	1 X Phosphate Buffered Saline (PBS), pH 4.0 [degas]	**100 mL**	37.0 ± 0.3°C	**None** [sample bottles to remain undisturbed in the water bath]
• For each sample preparation, **place one (1) Dexamethasone Punctum Plug** into a 125-mL polypropylene bottle.				

In Vitro Release Acceptance Criteria: ACCEPTABLE

The following in vitro release Acceptance Criteria are acceptable:

Time (Days)	% Release
0.21	(b) (4)%

1	(b) (4) %
2	%
3	%
4	NL (b) (4) %

(b) (4)

From the Biopharmaceutics perspective, NDA 208742 for Dexamethasone Extended Release Insert is recommended for **APPROVAL.**

E. Novel Approaches: None

F. Any Special Product Quality Labeling Recommendations: None

G. **Life Cycle Knowledge Information**

From Initial Risk Identification			Review Assessment		
Attribute/ CQA	Factors that can impact the CQA	Initial Risk Ranking	Risk Mitigation Approach	Final Risk Eval.	Lifecycle Considerations Comments
Sterility	• Formulation • Container closure[1] • Process parameters • Scale/equipment • Site	H	No preservative (b) (4) (b) (4) sterilization has been validated. Sterility assurance is included in the release drug product specification.	H	Post-approval stability protocol[2] will test sterility.

Endotoxin Pyrogen	• Formulation • Container closure[1] • Process parameters	H	Endotoxin testing will be performed at release.	L	Endotoxin testing will be performed at release on stability.
Assay (API), stability	• Formulation • Container closure[1] • Raw materials	L	Robust analytical method validated for assay; no trend on stability; levels remain within the proposed specification. Label claim will be delivered.	L	
Assay (preservative)	• Formulation • Container closure[1] • Process parameters • Scale/equipment	L	No preservative. Single use.	L	
Uniformity of Dose	• Formulation • Container closure[1] • Process parameters • Scale/equipment	H	Content uniformity is included in the drug product release specification.	L	
Osmolality	• Formulation • Container closure[1] • Process parameters • Scale/equipment	L	The drug product is an insert. Not relevant.	L	
pH	• Formulation • Container closure[1] • Process parameters • Scale/equipment	L	The drug product is an insert. Not relevant.	L	
Particulate matter	• Formulation • Container closure[1] • Process parameters • Scale/equipment	M	Per ophthalmic product requirements, particulate matter is controlled in the drug specification with no for foreign particulate matter.	L	
In vitro drug release	• Formulation	H	An in vitro release test is included in the drug product specifications. The acceptance criteria were modified to better capture the release profile. The in vitro release method can detect changes in the drug product that occur upon storage at a higher temperature. In addition, the in vitro release method is discriminating with regard to the drug loading in the gel.	L	

1 Stability studies demonstrate container closure compatibility with the drug product for all quality attributes.

2 Post-approval stability protocol provides for testing of all quality attributes.

Primary Quality Review

ASSESSMENT OF THE BIOPHARMACEUTICS INFORMATION

Adequate. Refer to Review #1 dated on 6/17/2016.

ASSESSMENT OF MICROBIOLOGY

Adequate. Refer to Review #1 dated on 6/17/2016.

ASSESSMENT OF ENVIRONMENTAL ANALYSIS

Adequate. Refer to Review #1 dated on 6/17/2016.

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Vidya Pai

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Date: 7/05/2017 11:18:41AM
GUID: 53b581d20000464509a65e37ec9ad4a2

Derek Smith

Digitally signed by Derek Smith
Date: 7/05/2017 11:36:52AM
GUID: 508da7480002bfe5d5fe14a12da3599d

Chunchun Zhang

Digitally signed by Chunchun Zhang
Date: 7/05/2017 12:40:28PM
GUID: 51269608000064178e75377202fe6c5d

Recommendation: Complete Response

NDA 208742
Review #1
June 17, 2016

Drug Name/Dosage Form	Dexamethason (b) (4) Insert
Strength	0.4 mg
Route of Administration	Intracanalicular
Rx/OTC Dispensed	Rx
Applicant	Ocular Therapeutix Inc
US agent, if applicable	N/A

SUBMISSION(S) REVIEWED	DOCUMENT DATE
Original	24-Sep-2015
Amendment	07-Dec-2015
Amendment	22-Dec-2015
Amendment	14-Jan-2016
Amendment	21-Mar-2016
Amendment	01-Apr-2016
Amendment	21-Apr-2016
Amendment	05-May-2016
Amendment	25-May-2016
Amendment	26-May-2016
Amendment	7-Jun-2016
Amendment	13-Jun-2016

Quality Review Team

DISCIPLINE	Reviewer	BRANCH/DIVISION
Drug Substance	Anamitro Banerjee	ONDP/DNDPI/NDPBII
Drug Product	Chunchun Zhang	ONDP/DNDP-I/Branch III
Process	Vidya Pai	OPF/DIABIII
Microbiology	Daniel Schu	OPF/DMA/MABIII
Facility	Aditi Thakur, Vidya Pai	OPF/DIA/DIABII, DIABIII
Biopharmaceutics	Om Anand	ONDP/DB/Branch I
Regulatory Business Process Manager	Erin Andrews	OPRO/DRBPMI/RBPMBI
Application Technical Lead	Chunchun Zhang	ONDP/DNDP-I/Branch III
Laboratory (OTR)	NA	
ORA Lead	Paul Perdue	ORA/OO/OMPTO/DMPTPO/MDTP
Environmental Assessment (EA)	Chunchun Zhang	ONDP/DNDP-I/Branch III

Table of Contents

Quality Review Data Sheet

1. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	STATUS	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	Type II	(b) (4)	(b) (4)	Adequate	May 25, 2016	LoA: 4/11/2012. Reviewed by Anamitro Banerjee.

B. Other Documents: *IND, RLD, or sister applications*

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	114720	This product during IND development

2. CONSULTS:

DISCIPLINE	STATUS	RECOMMENDATION	DATE	REVIEWER
Biostatistics	NA			
Pharmacology/Toxicology	Adequate		3/11/2016	Andrew McDougal
CDRH	NA			
Clinical	NA			
Other	NA			

Executive Summary

I. Recommendations

Satisfactory information and responses have been submitted to support the quality of the drug substance, drug product, biopharmaceutics and quality micro aspects.

However, the outcome of the most recent inspection of drug product manufacturing facility (Ocular Therapeutix Inc) has resulted in Office of Process and Facilities recommending Withhold. Therefore, NDA 208742 is recommended for Complete Response from Product Quality perspective. Additionally, there are some deficiencies in the process which are non CR issues.

Labeling recommendations from the Product Quality perspective will be provided to the OND PM for consideration during final labeling.

A. Recommendation and Conclusion on Approvability

1. Summary of Complete Response issues: As described above.

2. Action letter language, related to critical issues such as expiration date :
   The following CR statements about the unacceptable manufacturing facility (Ocular Therapeutix Inc) should be included in the CR letter:
   1. *During a recent inspection of the **Ocular Therapeutix, Inc., FEI#3008477155**, manufacturing facility for this application, our field investigators conveyed deficiencies to the representatives of this facility. Satisfactory resolution of these deficiencies is required before this application may be approved.*

   The following non-CR comments should be included in the CR letter:
   1. *The submission includes updates to critical material attributes [(b) (4)]), critical process paramet [(b) (4)]), in-process control [(b) (4)] and yield limits. The supporting test results for the metrics above were not provided for registration, stability and proposed PQ batches. Your response to information requests has referenced two subsequent lots, Lot No. 03241602 and 04211605 [(b) (4)] unit scale, taken through all process steps) generated using the intended commercial process parameters. While you have provided batch size and yield on these lots, the information provided does not include all the relevant details (e.g. batch manufacturing records, in-process test results). Provide these details to support that your updated production and process controls assure that in-process materials and finished product meet the predetermined quality requirements.*

2. *The submission includes limited information on the intended scale-up strategy beyond the current commercial scal (b) (4) units). In light of the process complexity, unique dedicated custom-made equipment, extent of manual operations, scale-up for any process operation (e.g. (b) (4) beyond the stated commercial scale should be submitted as a Prior Approval Supplement (PAS).*

3. Benefit/Risk Considerations: Not applicable for CR.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

II. Summary of Quality Assessments

A. Drug Substance [Dexamethasone] Quality Summary

The applicant cross-referenced the CMC information for the drug substance to DMF (b) (4) DMF (b) (4) was found adequate by Anamitro Banerjee on 5/25/2016.

B. Drug Product [Dexamethasone Insert] Quality Summary

Dexamethasone intracanalicular insert drug product i (b) (4) yello (b) (4) with no visible foreign particulate matter 3mm cylindrical shaped insert in a foam inser (b) (4) within (b) (4) foil pouch.

All excipients used in the formulation are adequately qualified. No novel excipients are used in the formulation. The drug product specification includes tests for appearance, identification, assay, impurity, dry dimension, content uniformity, expansion, equilibrium diameter, in vitro release, water content, visibility, endotoxin and sterility. The specification is acceptable. All analytical methods are described in reasonable detail and have been adequately validated. Additionally, all microbiology related issues concerning the drug product have been satisfactorily resolved.

Batch analyses are provided for 3 registration batches and one commercial batch of drug products in the commercial container closure system a (b) (4) units scales (commercial scale (b) (4) units). All batches complied with the proposed specification.

Eighteen months of stability data for one registration batch and twelve months of stability data for the other two registration batches at long term condition (5°C) are provided at 74% of commercial scale. No accelerated stability data is submitted in the NDA. There is no trend observed on all the test parameters when the drug products were stored at long term storage condition (5°C). These results which included statistical analysis supports both the expiration dating period and storage statement listed below.

1. Strength: 0.4 mg
2. Description/Commercial Imag (b) (4) yellow (b) (4), with no visible foreign particulate matter 3mm cylindrical shaped insert.
3. Summary of Product Design: Dexamethasone intracanalicular insert

4. List of Excipients: See review notes, below.
5. Process Selection (Unit Operations Summary)
   a. Sterilization processes of the drug product, as applicable
   b. [redacted (b) (4)]
6. Container Closure: In a foam inser [redacted (b) (4)] within a [redacted (b) (4)] [redacted (b) (4)] foil pouch.
7. Expiration Date & Storage Condition [redacted (b) (4)] months with the storage statement of stored 2°C – 8°C and a cautionary statement, "protect from light".
8. List of co-packaged components: None

C. Summary of Drug Product Intended Use

Proprietary Name of the Drug Product	DEXTENZA
Non Proprietary Name of the Drug Product	Dexamethasone intracanalicular insert
Non Proprietary Name of the Drug Substance	Dexamethasone
Proposed Indication(s) including Intended Patient Population	Treatment of ocular pain associated with ophthalmic surgery
Duration of Treatment	NA
Maximum Daily Dose	0.4 mg
Alternative Methods of Administration	NA

D. Biopharmaceutics Considerations

Dextenza™ [redacted (b) (4)] dexamethasone) Insert is indicated for the treatment of ocular pain associated with ophthalmic surgery. Dextenza is a dexamethasone intracanalicular insert drug product [0.4 mg strength] that is inserted into the canaliculus following ophthalmic surgery. The Biopharmaceutics review evaluated the acceptability

of the in vitro release method, the in vitro release acceptance criteria [redacted] (b) (4)

[redacted]

In Vitro Release Method: ACCEPTABLE

The following in vitro release method is acceptable:

Apparatus	Medium	Medium Volume	Temperature	Shaking/stirring
125-mL polypropylene bottle	1 X Phosphate Buffered Saline (PBS), pH 4.0 [degas]	**100 mL**	37.0 ± 0.3°C	**None** [sample bottles to remain undisturbed in the water bath]
• For each sample preparation, **place one (1) Dexamethasone Punctum Plug** into a 125-mL polypropylene bottle.				

In Vitro Release Acceptance Criteria: ACCEPTABLE

The following in vitro release Acceptance Criteria are acceptable:

Time (Days)	% Release
0.21	[redacted] (b) (4) %
1	[redacted] %
2	[redacted] %
3	[redacted] %
4	NLT [redacted] (b) (4) %

[redacted] (b) (4)

From the Biopharmaceutics perspective, NDA 208742 for Dexamethason [redacted] (b) (4) Insert is recommended for **APPROVAL.**

E. Novel Approaches: None

F. Any Special Product Quality Labeling Recommendations: None

G. Life Cycle Knowledge Information

From Initial Risk Identification			Review Assessment		
Attribute/ CQA	Factors that can impact the CQA	Initial Risk Ranking	Risk Mitigation Approach	Final Risk Eval.	Lifecycle Considerations Comments
Sterility	• Formulation • Container closure[1] • Process parameters • Scale/equipment • Site	**H**	No preservative [redacted] (b) (4) [redacted] sterilization ted. Sterility assurance is included in the release drug product specification.	**H**	Post-approval stability protocol[2] will test sterility.

Endotoxin Pyrogen	• Formulation • Container closure[1] • Process parameters	H	Endotoxin testing will be performed at release.	L	Endotoxin testing will be performed at release on stability.
Assay (API), stability	• Formulation • Container closure[1] • Raw materials	L	Robust analytical method validated for assay; no trend on stability; levels remain within the proposed specification. Label claim will be delivered.	L	
Assay (preservative)	• Formulation • Container closure[1] • Process parameters • Scale/equipment	L	No preservative. Single use.	L	
Uniformity of Dose	• Formulation • Container closure[1] • Process parameters • Scale/equipment	H	Content uniformity is included in the drug product release specification.	L	
Osmolality	• Formulation • Container closure[1] • Process parameters • Scale/equipment	L	The drug product is an insert. Not relevant.	L	
pH	• Formulation • Container closure[1] • Process parameters • Scale/equipment	L	The drug product is an insert. Not relevant.	L	
Particulate matter	• Formulation • Container closure[1] • Process parameters • Scale/equipment	M	Per ophthalmic product requirements, particulate matter is controlled in the drug specification with no for foreign particulate matter.	L	
In vitro drug release	• Formulation	H	An in vitro release test is included in the drug product specifications. The acceptance criteria were modified to better capture the release profile. The in vitro release method can detect changes in the drug product that occur upon storage at a higher temperature. In addition, the in vitro release method is discriminating with regard to the drug loading in the gel.	L	

1 Stability studies demonstrate container closure compatibility with the drug product for all quality attributes.

2 Post-approval stability protocol provides for testing of all quality attributes.

OVERALL ASSESSMENT AND SIGNATURES: EXECUTIVE SUMMARY

Application Technical Lead Signature:

NDA 208742 is recommended for Complete Response based on the withhold recommendation on drug product manufacturing facility by OPF.

Chunchun Zhang -S

Digitally signed by Chunchun Zhang -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Chunchun Zhang -S, 0.9.2342.19200300.100.1.1=2001178137
Date: 2016.06.17 12:44:05 -04'00'

Chunchun Zhang, Ph.D.; Acting CMC Lead; Branch 3; Division of New Drug Products I

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ASSESSMENT OF THE BIOPHARMACEUTICS INFORMATION

This is a 505 (b)(2) NDA submission for a dexamethasone intracanalicular insert drug product [0.4 mg strength]. Dextenza™ [1] (b) (4) dexamethasone)[2] Insert containing 0.4 mg dexamethasone, is indicated for the treatment of ocular pain associated with ophthalmic surgery. Dextenza is inserted into the canaliculus following ophthalmic surgery.

Review: The Biopharmaceutics review focuses on the evaluation and acceptability of

i. the in vitro drug release method and acceptance criteria, and
ii. (b) (4)

23. **Are the in-vitro dissolution test and acceptance criteria adequate for assuring quality control and consistent bioavailability of the drug product?**

23.1 What are the highlights of the chemistry and what are the physico-chemical properties of the drug substance and formulation of the drug product?

Dexamethasone is an anti-inflammatory 9-fluoro-glucocorticoid. (b) (4) dexamethasone, USP, is a white to practically white, odorless crystalline powder practically insoluble in wate (b) (4) (b) (4)

The proposed product is a single administration sterile dosage form which consists of (b) (4) dexamethasone and 4-arm polyethylene glycol (PEG) glutarate-trilysine hydrogel conjugated with fluorescein. The composition of Dextenza is listed in Table 23.1 below.

Table 23.1: Composition of Dextenza [dexamethasone, 0.4 mg intracanalicular depot]

Ingredient	Nominal Amount	Function
Active Pharmaceutical Ingredient (API)		
Dexamethasone, Micronized, USP	(b) (4) %	API
(b) (4)	(b) (4)	
4-arm 20K PEG SG	(b) (4) %	(b) (4)
Trilysine Acetate		
NHS-Fluorescein	%	
Sodium Phosphate Dibasic, USP		
Sodium Phosphate Monobasic, (b) (4) USP		

[1] In the submission the Applicant referred to this as sustained release dexamethasone
[2] It is also referred as the Dexamethasone Punctum Plugs (OTX-DP) in the submission.

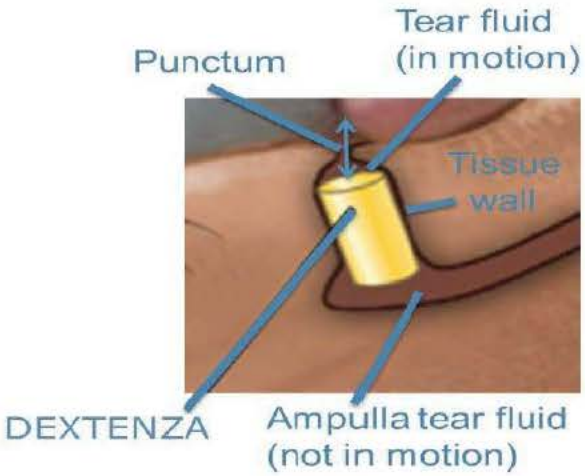
Hydrogel Matrix: The hydrogel matrix components of Dextenza are readily soluble in aqueous solutions (b) (4)

(b) (4)

In the eye's canaliculus, after Dextenza hydrogel is hydrolyzed, the fluorescent PEG material drains through the lacrimal drainage system (b) (4)

(b) (4)

Figure 23.1: Anatomical representation of Dextenza placement



(b) (4)

[redacted]

[3] Chapter 1151

(b) (4)

- Dextenza™ i (b) (4) resorbable drug product with a hydrogel (b) (4) and dexamethasone. The Applicant claims that the hydrogel (b) (4)e is designed to remain in the vertical canaliculus for 30 days (b) (4) (b) (4) Over this time and through hydrolysis, Dextenza softens, liquefies and is cleared through the nasolacrimal duct. Dextenza is indicated for the treatment of ocular pain associated with ophthalmic surgery.

- The Listed Drug [LD] products which are the basis of this NDA submission are Maxidex [NDA 013422; Dexamethasone Ophthalmic Suspension/Drops 0.1 %]; and Decadron [NDA 011984; Solution/Drops; Ophthalmic, Otic; Eq 0.1% Phosphate]. Decadron is listed in the discontinued section of the electronic Orange Book[4].
  In the Dosage and Administration section of the Maxidex label it is stated "*One or two drops topically in the conjunctival sac(s). In severe disease, drops may be used hourly, being tapered to discontinuation as the inflammation subsides. In mild disease, drops may be used up to four to six times daily*".
  The Dextenza proposed label states (b) (4) (b) (4)

- Study OTX-14-009 was conducted to evaluate the plasma pharmacokinetics of Dextenza as (b) (4)(dexamethason (b) (4) when placed in the canaliculus of the eyelid of healthy subjects. Plasma concentrations were below the lower limit of quantitation (LLOQ = 0.05 ng/mL) at all time-points in five of the 16 subjects. Additionally, plasma concentrations were below the LLOQ at the Day 15, 22 and 29 visits in the remaining subjects. Plasma dexamethasone concentrations from 11% of samples (21 of 190) were above the LLOQ, ranging from 0.05 ng/mL to 0.81 ng/mL. This study demonstrated that systemic exposure to dexamethasone is negligible with the use of Dextenza. This study indicates that there is no dose dumping from Dextenza.

- The Applicant also claimed that the systemic exposure to dexamethasone from Dextenza is similar to that reported with intravitreal administration of dexamethasone 0.7 mg [Ozurdex US product information] and following topical ocular administration of dexamethasone 0.1% suspension [Tobradex ST product information and Weijtens et al., 2002), and several fold lower than that following a single oral administration of 7.5 mg dexamethasone.

- One phase 2 (OTX-12-002) and two phase 3 (OTX-13-002 and OTX-14-003) studies were conducted to evaluate the efficacy and safety of Dextenza for the

[4] http://www.accessdata.fda.gov/scripts/cder/ob/docs/tempai.cfm

treatment of ocular pain and inflammation following cataract surgery. The primary efficacy endpoints for the three trials were the proportion of subjects with absence of anterior chamber cells in the study eye (at the Day 8 Visit in OTX-12-002; at the Day 14 Visit in OTX-13-002 and OTX-14-003) and the proportion of subjects with absence of ocular pain in the study eye (at the Day 8 Visit in all three trials). Dextenza was demonstrated to be superior to PVPP [Placebo Vehicle Punctum Plug] for the treatment of ocular pain following cataract surgery at the primary endpoint visit on Day 8

- The release of dexamethasone from Dextenza was studied in a Beagle dog model with a dexamethasone punctum plug containing 372 µg dexamethasone (TP0183/TR0183). Results of this study in dogs demonstrated a tapered delivery of dexamethasone into the tear fluid over the course of 28 days.

- In vitro release profiles for Dextenza [Figure 23.16] indicate a slow and (b) (4) release.

Reviewer's Initial Assessment (b) (4): Satisfactory

(b) (4)

a (b) (4)

b.) The dosing frequency for Dextenza™ (b) (4) dexamethasone) 0.4 mg Intracanalicular Insert is markedly different from the IR product [Maxidex] [the proposed dosing for Dextenza is once in 30 days vs. four to six times daily for Maxidex].

c.) There is no indication of dose dumping from Dextenza.

d.) In a Beagle dog study, the release of dexamethasone from Dextenza into the tear fluid was noticed over the course of 28 days.

e.) The in vitro release of dexamethasone, which is water soluble (b) (4) (b) (4)

(b) (4)

23.4 What is the proposed in vitro release method?

The proposed in vitro release method[5] is presented below in Table 23.2:

Table 23.2: Proposed in vitro release method

Apparatus	Medium	Medium Volume	Temperature	Shaking/stirring
125-mL polypropylene bottle	Phosphate Buffered Saline (PBS), pH 4.0 [degas]	**100 mL**	37.0 ± 0.3°C	**None** [sample bottles to remain undisturbed in the water]

Punctum Plug Sample Preparations – (n (b) (4)*).

- (b) (4)
- add 100 mL of buffer solution to each bottle and cap tightly. Gently invert and swirl the bottle to ensure all plugs are wet.
- place sample bottles into water baths at 37.0 ± 0.3°C. Place each replicate in separate bath.
- Allow the sample bottles to remain undisturbed in the water bath until sampled.
- For each time point, gently invert and swirl samples to ensure a homogenous mixture and return to water bath. Remove 1.0 mL of the supernatant (sampling 1/3 way down the bottle) and transfer to a HPLC vial.
- Replace 1.0 mL of heated buffer into the polypropylene sample bottle. Cap tightly. Gently swirl the bottle to re-suspend the plugs. The samples are only to be removed from the bath when mixing.

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[5] TM60021

23.6 What information is available to support the robustness (e.g. linearity, accuracy, etc.) of the in vitro release methodology?

The Applicant demonstrated the specificity, linearity, range, accuracy, precision method repeatability, precision sample repeatability, intermediate precision, limit of detection (LOD), limit of quantitation (LOQ), sample solution stability, standard solution stability, robustness and system suitability of the analysis for dexamethasone in vitro release.

Table 23.3 Validation Results for M60021 - In Vitro Release method

Validation Parameter	Requirements
Specificity	Resolution > 1
Linearity	$R^2 \geq 0.998$
Accuracy	Recovery 100 ± 25%
Precision	RSD ≤ 30.0%
Repeatability	RSD ≤ 30.0%
Intermediate Precision	RSD ≤ 30%
LOD	SN > 3.0
	RSD of Area ≤ 20%
LOQ	SN > 10.0
	RSD of Area ≤ 10%
Standard Stability	Recovery 100 ± 5%
Sample Stability	Recovery 100 ± 5%
Robustness*	Variable

Reviewer's Note: Upon completion of the Pre-NDA approval inspectio (b) (4) Facility, the FDA issued Form 48 (b) (4)

(b) (4)

(b) (4)

Reviewer's Assessment: Satisfactory

Though this Reviewer believes that th (b) (4) process is not the most appropriate metho (b) (4) the Applicant explained that the method is well established through SOPs. The Applicant's response is reasonable and acceptable.

23.7 What data are available to support the discriminating power of the in vitro release method?

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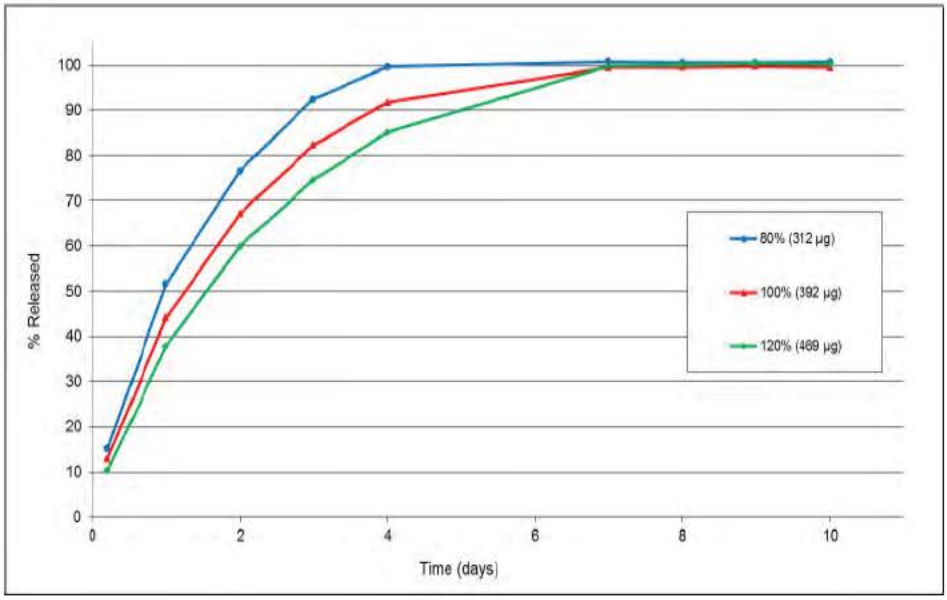
(b) (4)

[8] Analytical Data Processing, Review and Filing. Reprocessing

Applicant's Response [dated: 05/26/2016]: In response to the above request, the Applicant conducted additional experiments using Dextenza drug product with a 20% variance in the 394 µg drug load i.e. 80%, 100%, and 120% drug load. The drug release results are provided in Figure 23.16. The Applicant stated that the data show that the in vitro release method is capable of providing an indication of gross drug over or under loading.

Figure 23.16: In vitro release from dexamethasone punctum plugs at various dose levels of dexamethasone [80%, 100%, and 120% drug load]



<u>Reviewer's Assessment of Applicant's Responses</u> [dated: 03/21/2016, 4/21/2016 and 5/26/2016]: Satisfactory

The Applicant demonstrated that the proposed drug release method has a reasonable discriminating ability with regard to formulations varying in the drug loading [**80%, 100%, and 120% drug load**]. The Applicant's response is reasonable and acceptable.

<u>Reviewer's Overall Assessment of in vitro drug release method:</u> Satisfactory
Though, the in vitro drug release method is not discriminating with regard to the CMAs and the CPPs and the particle size of the drug substance, the method can detect changes that may occur if the product is stored at higher temperatures than the recommended storage temperature. In addition, the method can pick up the variation in the drug loading. Considering the fact that this is a very special dosage form where the movement of the fluid is limited, this Reviewer believes that the proposed method [with one plug per bottle] can be used as a quality control tool. Therefore, the following in vitro drug release method is found acceptable:

Apparatus	Medium	Medium Volume	Temperature	Shaking/stirring
125-mL polypropylene bottle	Phosphate Buffered Saline (PBS), pH 4.0 [degas]	**100 mL**	37.0 ± 0.3°C	**None** [sample bottles to remain undisturbed in the water bath]
• for each sample preparation, **place one (1) Dexamethasone Punctum Plug** into a 125-mL polypropylene bottle.				

23.8 What are the proposed in vitro release acceptance criteria? Are the proposed in vitro release acceptance criteria adequate for assuring the consistent in vitro dissolution of the drug product?

The Applicant originally proposed the following acceptance criteria:

Table 23.7: Originally proposed acceptance criteria for Dextenza

DEXTENZA (# of lots)	Time (days)	Specification Range	Minimum	Maximum
(b) (4)				

The acceptance criteria for in vitro release were based on in vitro drug release data from stability and clinical lots of Dextenza. Testing was conducted according to the method [TM 60021] usin (b) (4) Dexamethasone punctum plugs into a 125-mL polypropylene bottle.

The original method [TM 60021], usin (b) (4) Dexamethasone punctum plugs into a 125-mL polypropylene bottle [100 mL of release medium], was found unacceptable [section 23.4]. In a response [dated: 04/21/2016], the Applicant conducted drug release testing o (b) (4) dosage units (b) (4) different punctum plugs in (b) (4) different bottles]. The drug release profiles are presented below in Figure 23.17.

(b) (4)

(b) (4)

Table 23.8[11]: Recommended in vitro release method for dexamethasone punctum plugs [Dextenza]

Apparatus	Medium	Medium Volume	Temperature	Shaking/stirring
125-mL polypropylene bottle	1 X Phosphate Buffered Saline (PBS), pH 4.0 [degas]	**100 mL**	37.0 ± 0.3°C	**None** [sample bottles to remain undisturbed in the water bath]

- for each sample preparation, **place one (1) Dexamethasone Punctum Plug** into a 125-mL polypropylene bottle.
- add 100 mL of buffer solution to each bottle and cap tightly. Gently invert and swirl the bottle to ensure all plugs are wet.
- place sample bottles into water baths at 37.0 ± 0.3°C. Place each replicate in separate bath.
- Allow the sample bottles to remain undisturbed in the water bath until sampled.
- For each time point, gently invert and swirl samples to ensure a homogenous mixture and return to water bath. **Re**move 1.0 mL of the supernatant (sampling 1/3 way down the bottle) and transfer to a HPLC vial.
- **Replace 1**.0 mL of heated buffer into the polypropylene sample bottle. Cap tightly. Gently swirl the bottle to re-suspend the plugs. The samples are only to be removed from the bath when mixing.

2. Your proposed drug release acceptance criteria are not supported by the data submitted and therefore not acceptable. We recommend that you implement the following drug release acceptance criteria:

Table 23.9: Recommended in vitro release Acceptance Criteria for dexamethasone punctum plugs [Dextenza]

Time (Days)	% Release
0.21	(b) (4) %
1	%
2	%
3	%
4	NL (b) (4) %

Please provide a revised drug product specification table and update your stability protocol accordingly.

Applicant's Response [dated: 6/09/2016]: The Applicant accepted the above stated in vitro release method and acceptance criteria. The Applicant also stated that this modified method will further be validated and this validation is likely to be completed on or about July 22, 2016. The Applicant also stated that validation is a pre-requisite to implementation of the new method for product release and stability assessment and the validation will be completed prior to release of any commercial Dextenza drug product.

[11] Note: Table # 23.8 and 23.9 are for reviewer purpose only

The Applicant also provide revised drug product specification table and stated that they have updated the stability protocol [TP0241] accordingly.

Reviewer's Assessment of the In Vitro Release Method and the Acceptance Criteria:
Acceptable

The Applicant accepted the recommended the Vitro Release Method [Table 23.8] and the Acceptance Criteria [Table 23.9] for dexamethasone punctum plugs [Dextenza] for release and stability testing.

23.9 Are all the strengths evaluated in the pivotal clinical trials? What data are available to support the approval of lower strengths?

N/A

23.10 Is there a request for a waiver of the submission of in vivo BE data (Biowaiver)? What is the purpose of the biowaiver request?

N/A

24. **Are the changes in the formulation, manufacturing process, manufacturing sites during the development appropriately bridged to the commercial product?**

A comparison of the formulations used in the Phase 2 clinical study [OTX-12-002], Phase 3 clinical studies [OTX-13-002, OTX-14-003, and OTX-14-009], and commercial production is provided below in Table 24.1.

Table 24.1: Comparison of Clinical and Commercial Formulations

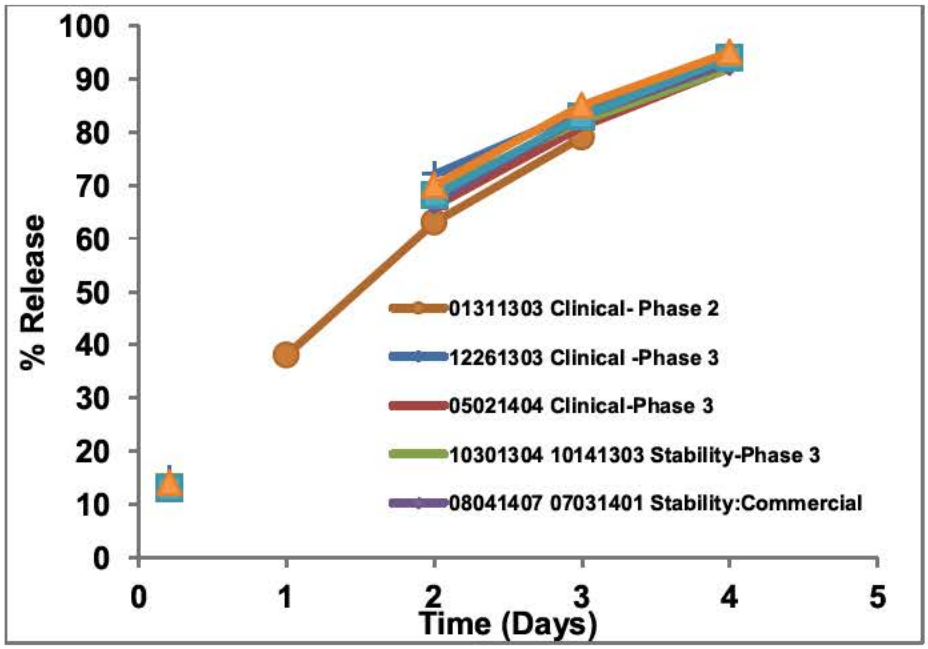
	Phase 2	Phase 3	Commercial
Formulation			
Dexamethasone	(b) (4)		
4-arm 20K PEG			
Sodium Dibasic Phosphate			
Sodium Monobasic Phosphate			
Trilysine Acetate			
NHS-Fluorescein			

There are two differences between the formulations provided[12] in Table 24.1:

a) (b) (4)

b)

Figure 24.1: In vitro release profiles comparison of Phase 2, Phase 3 and Commercial formulations of dexamethasone punctum plugs [Dextenza].



Reviewer's Assessment: Acceptable.

The Applicant provided comparative dissolution data supporting the bridging of the Phase 2, Phase 3 and commercial formulations.

Both pivotal clinical studies [OTX-13-002 and OTX-14-003] used the Phase 3 formulation. The Phase 3 and the commercial formulations are identical qualitatively but slightly different quantitatively; these quantitative differences are minor and were made

[12] The details of these comparisons are provided in in Section 3.2.P.2.3, Table 8 of the NDA.

(b) (4)The in vitro release profile comparisons are summarized in Figure 24.1. As presented above in Figure 24.1, the in vitro release performances of these batches used in the Phase 3 studies and the commercial batches are similar. Therefore, the bridging between the Phase 3 formulation and the commercial formulation is supported by the provided comparative in vitro release data.

OVERALL ASSESSMENT AND SIGNATURES: BIOPHARMACEUTICS

Reviewer's Assessment and Signature:

In Vitro Release Method: ACCEPTABLE

The following in vitro release method is acceptable:

Apparatus	Medium	Medium Volume	Temperature	Shaking/stirring
125-mL polypropylene bottle	Phosphate Buffered Saline (PBS), pH 4.0 [degas]	**100 mL**	37.0 ± 0.3°C	**None** [sample bottles to remain undisturbed in the water bath]

- for each sample preparation, **place one (1) Dexamethasone Punctum Plug** into a 125-mL polypropylene bottle.

In Vitro Release Acceptance Criteria: ACCEPTABLE

The following in vitro release Acceptance Criteria are acceptable

Time (Days)	% Release
0.21	(b) (4) %
1	%
2	%
3	%
4	NLT (b) (4) %

(b) (4)

Note that the CMC Reviewer may want to request that the Applicant changes the label t (b) (4)" in compliance with the USP nomenclature practices.

06/16/2016

Om Anand, Ph.D.
Biopharmaceutics Reviewer
Division of Biopharmaceutics/ONDP
Office of Pharmaceutical Quality

Secondary Review Concurrence and Signature:

I concur with Dr. Anand's assessment and recommendation.

06/16/2016

Elsbeth Chikhale, Ph.D.
Acting Biopharmaceutics Lead
Division of Biopharmaceutics/ONDP
Office of Pharmaceutical Quality

ASSESSMENT OF MICROBIOLOGY

25. Are the tests and proposed acceptance criteria for microbial burden adequate for assuring the microbial quality of the drug product?

Product Quality Microbiology Assessment

1. REVIEW OF COMMON TECHNICAL DOCUMENT-QUALITY (CTD-Q) MODULE 3.2: BODY OF DATA

S DRUG SUBSTANCE

The drug substance manufacturing process is not the subject of this product quality microbiology review as the drug product is [redacted] (b) (4) sterilized [redacted] (b) (4)

P DRUG PRODUCT

P.1 Description of the Composition of the Drug Product

- **Description of drug product**

  The subject drug product is a sustained release single administration sterile dosage form. It serves as [redacted] (b) (4) r dexamethasone. The drug product is a resorbable punctum plug consisting of a synthetic, dried, fluorescent PEG-based hydrogel designed to be inserted in the vertical canaliculus. Upon insertion (with forceps), the drug product swells on contact with moisture from the tear fluid until it is firmly secured in the canaliculus. It is designed to remain there for at least 30 days. Over this time period the drug product begins to soften and liquefy. Eventually it is then cleared through the nasolacrimal duct.

- **Drug product composition**

  The composition of the drug product is provided in Table 1 of Section 3.2.P.1 of the submission, which has been reproduced below.

Table 1: Composition of DEXTENZA Drug Product

Ingredient	Nominal Amount	Function	Manufacturer	Specification
Active Pharmaceutical Ingredient (API)				
Dexamethasone, Micronized, USP	(b) (4)	API	Pfizer DMF # 4524	PS 10-2004-002 IC 10-2004-002
(b) (4)				
4-arm 20K PEG SG			(b) (4)	PS 10-2001-001 IC 10-2001-001
Trilysine Acetate				PS 10-1001-003 IC 10-1001-003
NHS-Fluorescein				PS 10-2004-005 IC 10-2004-005
Sodium Phosphate Dibasic, USP				PS 10-1001-005 IC 10-1001-005
Sodium Phosphate Monobasic, (b) (4) USP				PS 10-1001-004 IC 10-1001-004

(b) (4) will be supplied from either (b) (4) facilities

- **Description of container closure system**

A singl (b) (4) is loaded in a foam insert, which is (b) (4) within (b) (4) (b) (4) foil pouc (b) (4) The foil pouch acts as a sure system are provided in Table 1 of Section 3.2.P.7, which has been reproduced below.

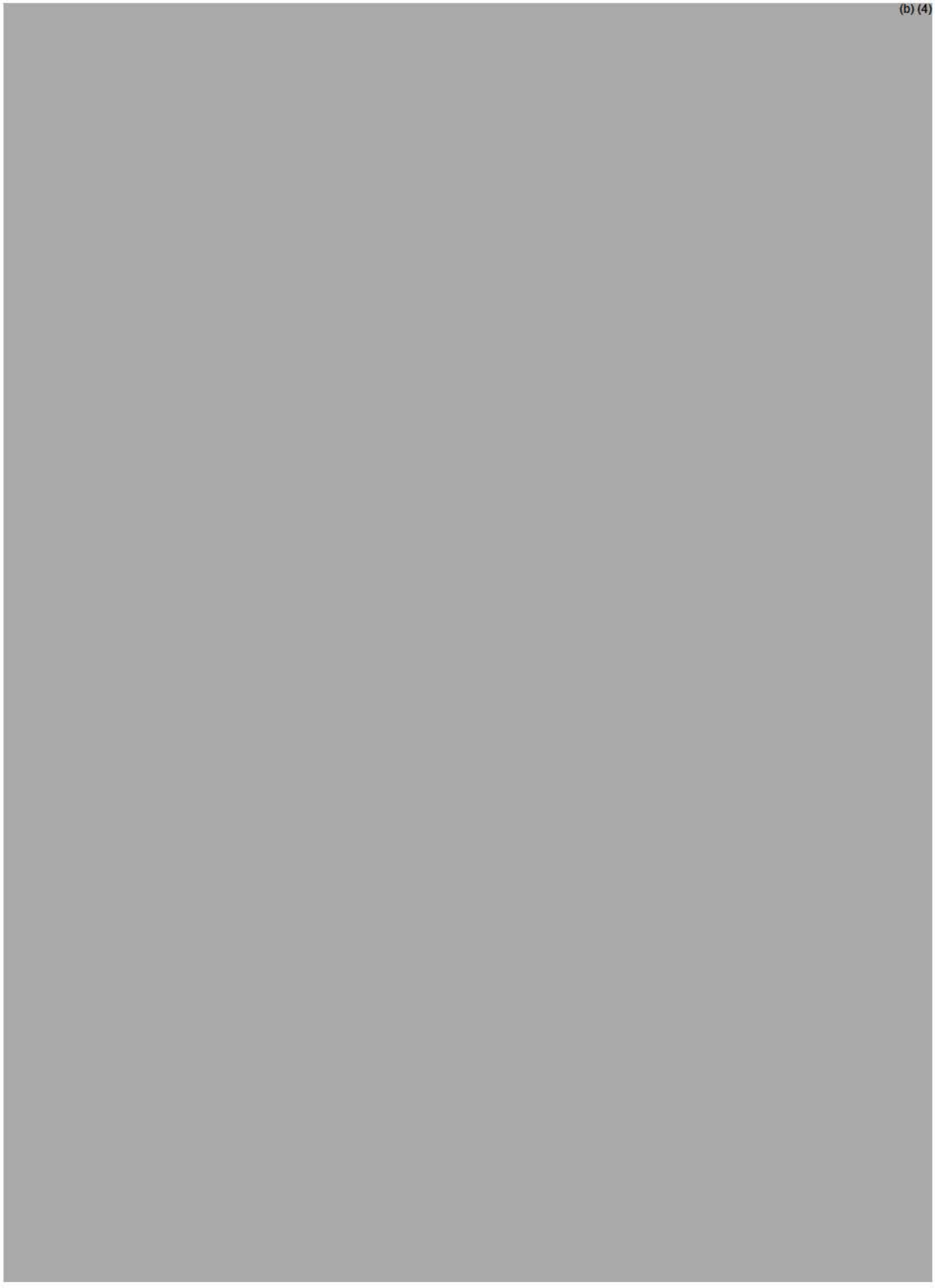
Table 1: DEXTENZA Container Closure System

Component	Description	Manufacturer	21 CFR Compliance
(b) (4)			
2.5" x 4.0" Peelable Foil Pouch	(b) (4)		(b) (4)

P.2 Pharmaceutical Development

(b) (4)

(b) (4)



(b) (4)

[redacted]

Acceptable

Reviewer's Comment

The applicant's verification of container closure integrity is consistent with regulatory expectations for a sterile pharmaceutical product.

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(b) (4)

[redacted]

P.8.3 Stability Data

(See Section 3.2.P.3.8.3)

18 months (Lot #10141303) and 12 months (Lots #07031401 and 0717404) of stability data are provided in support of the application. The three stability lots were manufactured at the proposed commercial batch production size o (b) (4) units. Stability studies were performed at 5°C, the proposed label storage condition. The studies were designed to provide data to support the minimum (b) (4) month expiration period and to mimic conditions of shipping, handling and administration of the proposed commercially manufactured drug product.

The subject drug product was determined to be incompatible with the ICH Q1A (R2) guidelines for accelerated storage evaluation of a refrigerated product as the drug produc (b) (4) (b) (4) resulting in observed differences in dissolution. The applicant states that when the drug product was examined under in vivo conditions, there was no difference between accelerated aging and non-aged drug product. It was therefore inferred

that the dissolution effect observed was an artifact of the storage condition. Therefore, studies under accelerated conditions were found unsuitable for the proposed drug product.

Reviewer's comment
Results of endotoxins testing for the three stability lots at time initial were provided in Tables 2-4 (pages 4-19) of Section 3.2.P.8.3. for the three stability lots, which were previously reviewed in Section P.5.2 Analytical Procedures-Endotoxin, and met the specification of < (b) (4) EU/Product.

Results of CCIT testing for both bubble test and seal strength were provided in Tables 2-4 (pages 4-19) of Section 3.2.P.8.3. All three lots met acceptance criteria for peel strength testing out to 18 months (Lot #10141303) and 12 months (Lots #08041407 and 08041408). For the bubble test, one sample did not meet the acceptance criteria for Lot #10141303. See Section 3.2.P.2.5 for details and a justification.

Acceptable

Reviewer's Comment
The applicant has met regulatory expectations with regard to the design of the stability testing program to support the drug product's microbiological quality throughout its shelf life. In addition, the stability data submitted to date support the microbiological quality of the subject drug product.

R REGIONAL INFORMATION

R.1 Executed Batch Record

(See 3.2.R.1 Regional Information Executed Batch Records)

All executed batch records from 2012, 2013, 2014 and 2015 are provided in the submission.

Acceptable

Reviewer's comment
The batch records confirm that validated sterilization processes were used for the manufacture of the exhibit batch.

2. REVIEW OF COMMON TECHNICAL DOCUMENT-QUALITY (CTD-Q) MODULE 1

A. PACKAGE INSERT

Storage temperature: 2 -8°C
Route of administration: For Intracanalicula (b) (4)
Dosage forms: Fluorescent yellow 3 mm cylindrical shaped 0.4 mg (b) (4) inserted into the canaliculus following ophthalmic surgery.

- The drug product releases a sustained and tapered dose for up to 30 days following insertion.
- The drug product is sterile, single-use only. Discard opened and unused product.

Acceptable

Reviewer's Comment
The applicant has met regulatory expectations with regard to the information related to issues of product quality microbiology that is provided in the product labeling.

3. LIST OF MICROBIOLOGY DEFICIENCIES AND COMMENTS: There are no microbiology deficiencies identified.

Reviewer's Assessment: Adequate

Data to support the process validation fo [redacted] sterilization of the subject drug product were provide [redacted] The application also included container-closure integrity studies in support of microbiology product quality sterility assurance [redacted] provides adequate sterility assurance for this sterile drug product.

2.3.P.7 Container/Closure System

26. Is the proposed container/closure system for the drug product validated to function as a barrier to microbial ingress? What is the container/closure design space and change control program in terms of validation?

Applicant's Response:

Reviewer's Assessment: Adequate

The applicant has provided sufficient results demonstrating the integrity of the container-closure as a microbial barrier.

A APPENDICES

A.2 Adventitious Agents Safety Evaluation

27. Are any materials used for the manufacture of the drug substance or drug product of biological origin or derived from biological sources? If the drug product contains material sourced from animals, what documentation is provided to assure a low risk of virus or prion contamination (causative agent of TSE)?

Applicant's Response: N/A

28. If any of the materials used for the manufacture of the drug substance or drug product are of biological origin or derived from biological sources, what drug substance/drug product processing steps assure microbiological (viral) safety of the component(s) and how are the viral inactivation/clearance capacity of these processes validated?

Applicant's Response: N/A

OVERALL ASSESSMENT AND SIGNATURES: MICROBIOLOGY

Reviewer's Assessment and Signature:
The Division of Microbiology Assessment has reviewed NDA 208742 for Dextenza™ (b) (4) Dexamethasone Intracanalicula (b) (4), and found the microbiology information adequate. From a microbiology perspective, NDA 208742 is recommended for **APPROVAL**.

Daniel J. Schu, Ph.D.
Microbiology Reviewer
OPQ/OPF/Division of Microbiology Assessment/Branch 3

Secondary Review Comments and Concurrence:
I concur with the microbiology assessment. NDA 208742 is recommended for **APPROVAL**.

Jessica G. Cole, Ph.D.
Microbiology Quality Assessment Lead (Acting)
OPQ/OPF/Division of Microbiology Assessment/Branch 3

ASSESSMENT OF ENVIRONMENTAL ANALYSIS

29. Is the applicant's claim for categorical exclusion acceptable?

30. Is the applicant's Environmental Assessment adequate for approval of the application?

Applicant's Response: The applicant requested a categorical exclusion from the requirement to prepare an environmental assessment (EA) under 21 CFR 25.31(b) on the grounds that the concentration at the point of entry into the aquatic environment is expected to be less than 1 ppb.

Reviewer's Assessment: Adequate.

OVERALL ASSESSMENT AND SIGNATURES: ENVIRONMENTAL

Reviewer's Assessment and Signature:

Adequate.
Chunchun Zhang, Ph.D.; Acting CMC Lead; Branch 3; Division of New Drug Product I.
May 20, 2016.

Secondary Review Comments and Concurrence:

I concur May 20, 2016.
Balajee Shanmugam, Ph. D.; Acting Branch Chief; Branch 3; Division of New Drug Product I.

I. Review of Common Technical Document-Quality (Ctd-Q) Module 1

Labeling & Package Insert

1. Package Insert

(a) "Highlights" Section (21CFR 201.57(a))

DEXTENZA™ (b) (4) dexamethasone (b) (4) insert) 0.4mg
Initial U.S. Approval: 1958

DOSAGE FORMS AND STRENGTHS

(b) (4) insert containing dexamethasone 0.4 mg.

Item	Information Provided in NDA	Reviewer's Assessment
Product title, Drug name (201.57(a)(2))		
Proprietary name and established name		Adequate
Dosage form, route of administration		Adequate
Controlled drug substance symbol (if applicable)		Not applicable
Dosage Forms and Strengths (201.57(a)(8))		
A concise summary of dosage forms and strengths		Adequate

Conclusion: Adequate. Labeling comments are marked up and highlighted in yellow in this review and will be finalized during team labeling review.

(b) "Full Prescribing Information" Section

 # 3: Dosage Forms and Strengths (21CFR 201.57(c)(4))

Fluorescent yellow 3 mm cylindrical shape (b) (4) insert containing dexamethasone 0.4 mg (b) (4)

Item	Information Provided in NDA	Reviewer's Assessment
Available dosage forms		Adequate
Strengths: in metric system		Adequate
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting, when applicable.		Adequate

Conclusion: Adequate. Labeling comments are marked up and highlighted in yellow in

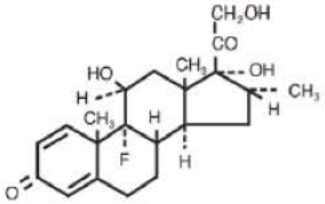
this review and will be finalized during team labeling review.

#11: Description (21CFR 201.57(c)(12))

11 DESCRIPTION

DEXTENZA (dexamethason [(b) (4)] inser [(b) (4)] is a fluorescent yellow 3 mm cylindrical shaped [(b) (4)] insert fo [(b) (4)]. DEXTENZA contains 0.4 mg dexamethasone in a polyethylene glycol (PEG) based hydrogel conjugated with fluorescein.

The active ingredient is represented by the chemical structure:



The chemical name for dexamethasone is 9-Fluoro-11β,17,21-trihydroxy-16α-methylpregna-1,4-diene- 3,20-dione. It has a molecular formula of $C_{22}H_{29}FO_5$ and a molecular weight of 392.47 g/mol. Dexamethasone is a crystalline powder.

Each DEXTENZA contains: **Active ingredients:** 0.4 mg dexamethasone; **Inactive ingredients**: 4-arm 20K polyethylene glycol (PEG) succinmidyl glutarate, trilysine acetate, NHS-fluorescein, sodium phosphate dibasic, sodium phosphate monobasic, water for injection.

Item	Information Provided in NDA	Reviewer's Assessment
Proprietary name and established name		Adequate
Dosage form and route of administration		Adequate
Active moiety expression of strength with equivalence statement for salt (if applicable)		Adequate
Inactive ingredient information (quantitative, if injectables 21CFR201.100(b)(5)(iii)), listed by USP/NF names.		Adequate
Statement of being sterile (if applicable)		Adequate
Pharmacological/ therapeutic class		Not applicable
Chemical name, structural formula, molecular weight		Adequate
If radioactive, statement of important nuclear characteristics.		Not applicable
Other important chemical or physical properties (such as pKa, solubility, or pH)		Not applicable

Conclusion: Adequate. Labeling comments are marked up and highlighted in yellow in this review and will be finalized during team labeling review.

#16: How Supplied/Storage and Handling (21CFR 201.57(c)(17))

DEXTENZA is supplied sterile in a foam carrier within a foil laminate pouch.
DX-2004-10 Carton containing 10 pouches **NDC** XXXX-XXXX-XX
(b) (4)

Do not use (b) (4) has been damaged or broken.
DEXTENZA is intended for single use only (b) (4)
Storage: Store refrigerated, between 2°C and 8°C (36°F and 46°F). Protect from light.

Item	Information Provided in NDA	Reviewer's Assessment
Strength of dosage form		Adequate
Available units (e.g., bottles of 100 tablets)		Adequate
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number		Adequate
Special handling (e.g., protect from light, do not freeze)		Adequate
Storage conditions		Adequate

Manufacturer/distributor name listed at the end of PI, following Section #17

Ocular Therapeutix, Inc.
Bedford, MA 01730 USA
(b) (4)

Item	Information Provided in NDA	Reviewer's Assessment
Manufacturer/distributor name (21 CFR 201.1)		Adequate

Conclusion: Adequate.

2. Container and Carton Labeling

1) Immediate Container Label

Reviewer's Assessment:

Item	Comments on the Information Provided in NDA	Conclusions
Proprietary name, established name (font size and prominence (21 CFR 201.10(g)(2))		Adequate
Strength (21CFR 201.10(d)(1); 21.CFR 201.100(b)(4))		Adequate
Route of administration 21.CFR 201.100(b)(3))		Adequate
Net contents* (21 CFR 201.51(a))		Adequate
Name of all inactive ingredients (Quantitative ingredient information is required for injectables) 21CFR 201.100(b)(5)**		Missing (only PEG conjugate is included).
Lot number per 21 CFR 201.18		Adequate
Expiration date per 21 CFR 201.17		Adequate
"Rx only" statement per 21 CFR 201.100(b)(1)		Adequate
Storage (not required)		Adequate
NDC number (per 21 CFR 201.2) (requested, but not required for all labels or labeling), also see 21 CFR 207.35(b)(3)		Adequate
Bar Code per 21 CFR 201.25(c)(2)***		Adequate
Name of manufacturer/distributor (21 CFR 201.1)		Adequate
Others		

*21 CFR 201.51(h) A drug shall be exempt from compliance with the net quantity declaration required by this section if it is an ointment labeled ''sample'', ''physician's sample'', or a substantially similar statement and the contents of the package do not exceed 8 grams.

**For solid oral dosage forms, CDER policy provides for exclusion of "oral" from the container label

**Not required for Physician's samples. The bar code requirement does not apply to prescription drugs sold by a manufacturer, repacker, relabeler, or private label distributor directly to patients, but versions of the same drug product that are sold to or used in hospitals are subject to the bar code requirements.

Conclusion: Adequate. All the inactive ingredients should be included. Labeling comments are marked up and highlighted in yellow in this review and will be finalized during team labeling review.

Comments to the applicant:

1. Storage conditions: "Store refrigerated, between 2°C and 8°C (36˚F and 46˚F). Protect from light".
2. The full name should read: DEXTENZA (dexamethason (b) (4) insert) 0.4mg.
3. The inactive ingredients should be 4-arm 20K polyethylene glycol (PEG) succinmidyl glutarate, trilysine acetate, NHS-fluorescein, sodium phosphate dibasic, sodium phosphate monobasic, water for injection.
4. DEXTENZA (b) (4) should be DEXTENZA insert.
5. Delete (b) (4)

2) Carton Labeling

(b) (4)

Item	Comments on the Information Provided in NDA	Conclusions
Proprietary name, established name (font size and prominence (FD&C Act 502(e)(1)(A)(i), FD&C Act 502(e)(1)(B), 21 CFR 201.10(g)(2))		Adequate
Strength (21CFR 201.10(d)(1); 21.CFR 201.100((d)(2))		Adequate
Net contents (21 CFR 201.51(a))		Adequate
Lot number per 21 CFR 201.18		Adequate
Expiration date per 21 CFR 201.17		Adequate
Name of all inactive ingredients (except for oral drugs); Quantitative ingredient information is required for injectables)[201.10(a), 21CFR201.100(d)(2)]		Missing (only PEG conjugate is included).
Sterility Information (if applicable)		Adequate
"Rx only" statement per 21 CFR 201.100(d)(2), FD&C Act 503(b)(4)		Adequate
Storage Conditions		Adequate
NDC number (per 21 CFR 201.2) (requested, but not required for all labels or labeling), also see 21 CFR 207.35(b)(3)		Adequate
Bar Code per 21 CFR 201.25(c)(2)**		Adequate
Name of manufacturer/distributor		Adequate
"See package insert for dosage information" (21 CFR 201.55)		Adequate
"Keep out of reach of children" (optional for Rx, required for OTC)		Not applicable
Route of Administration (not		Adequate

required for oral, 21 CFR 201.100(d)(1) and (d)(2))		

Conclusion: Adequate. All the inactive ingredients should be included. Labeling comments are marked up and highlighted in yellow in this review and will be finalized during team labeling review.

Comments to the applicant:

1. Storage conditions: "Store refrigerated, between 2°C and 8°C (36°F and 46°F). Protect from light".
2. The full name should read: DEXTENZA (dexamethason (b) (4). insert) 0.4mg.
3. The inactive ingredients should be 4-arm 20K polyethylene glycol (PEG) succinmidyl glutarate, trilysine acetate, NHS-fluorescein, sodium phosphate dibasic, sodium phosphate monobasic, water for injection.
4. DEXTENZA (b) (4) should be DEXTENZA insert
5. Delet (b) (4)

OVERALL ASSESSMENT AND SIGNATURES: LABELING

Reviewer's Assessment and Signature:

Adequate.
Chunchun Zhang, Ph.D.; Acting CMC Lead; Branch 3; Division of New Drug Product I.
May 20, 2016.

Secondary Review Comments and Concurrence:

I concur May 20, 2016.
Balajee Shanmugam, Ph. D.; Acting Branch Chief; Branch 3; Division of New Drug Product I.